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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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CIBA SPECIALTY CHEMICALS CORPORATION
PATENT DEPARTMENT
540 WHITE PLAINS RD
P O BOX 2005
TARRYTOWN, NY 10591-9005

EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/522,925	HOLZL ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 8-21* is/are rejected.

7)☐ Claim(s) *4-7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/24/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment which included amendment to claims 3, 5, and 10-19, filed on 1/25/2005, is made or record. Claims 1-21 are pending.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on 3/24/2005, are made of record.

Drawings

Specification has no Brief Description o the Drawing.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, and 11-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim.

1. Recitation of the term "either claim 1" renders claim 3 indefinite as it is not clear what is intended. Deletion of "either" is suggested.
2. Claims 11-19 provide for the use of a compound of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Note dependent claim 11-19 relates to use of the compound

of claim1 while claim 10 on which claims 11-19 are dependent relates to method treatment which has relevance on the uses claimed in claims 11-19. Hence claims 11-9 are treated as "use" claims.

3. Recitation of "compound of formula Ia according to claim 1" in process claims 8 and claim 9 renders these claims indefinite as there is no compound of formula Ia in claim1. It is not clear what is intended.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compound of formula Ia wherein the variable groups R_2 is hydrogen and R_3 is hydrogen, does not reasonably provide enablement for compound of formula Ia wherein the R_2 is hydrogen and R^3 is C_1alkyl, C_6-C_{20} alkyl, C_3-C_7 cycloalkyl, C_1-C_{20} perfluoroalkyl, C_1-C_{20} alkyl-carbonyl, C_3-C_7 cycloalkyl-carbonyl, C_1-C_{20} perfluoroalkyl-carbonyl and phenylcarbonyl with a given R′ choice as C_1-C_4 alkyl and with R^3 bearing reactive carbonyl functional group which is susceptible to the step involving acylation and the step involving reduction with BH_3-SMe_2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply: These claims are rejected based on the formula Ia.

In evaluating the enablement question, following factors are considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. The nature of the invention and the state of the prior art:

The invention of claim 8 is drawn to a process of making compound of formula Ia which involves condensation of pyridylamidine (Ib) with cyanoimidate (Ic) to arrive at Id which further acylated with R'CO-O-COR' to give product Id which then reduced with BH_3-SMe_2 to arrive at the final product of formula Ia.

The invention of claim 9 is drawn to a condensation of compound of formula Ig, namely pyridylacylimidate with compound of formula 1h namely a guanidine to obtain compound of formula Ia. Specification is not adequately enabled as to how to make compounds of formula (Ia) with above said choice of R_3 groups based on the choices of R' and with R_3 choices bearing reactive carbonyl functional groups which are either susceptible to condensing reaction of claim 8 and 9 and/or reduction step using BH_3-SMe_2 of claim 8 for the following reasons. First of all, with a given choice of R' as C_1-C_4 alkyl, it is not possible to arrive at various choices of R_3. This is clearly an error in the process shown in claim 8. Secondly, even if the R' choices are corrected to include all R_3 choices. The process of reduction would yield an additional "CH_2" group derived from CO

group of the amido group of formula Ie and this would still pose an issue. Particularly if R_3 is cyclalkyl, the process would lead cycloalklyl-CH_2 compound not the claimed cycloalkyl compound. Thirdly, the condensation reaction to build the triazine ring in claims 8 and 9 depend on the reaction of an amino group with a masked carbonyl as in formula Ic or a carbonyl group as in formula Ig and hence of carbonyl group in the starting material as permitted in R_3 choices would also react under the conditions of the condensation reaction. Finally, the carbonyl groups in R_3 would also undergo facile reduction with BH_3-SMe_2. Specification offers no teachings or suggestion as to how to perform the said process of claim 8 and claim 9 with above said limitations and in presence of the reactive carbonyl groups. Thus, presence of such reactive groups are chemically incompatible the process of condensation and BH_3-SMe_3 embraced in the instant claims.

2. The predictability or lack thereof in the art:

Hence the process as applied to the above-mentioned compounds claimed by the applicant is not an art-recognized process and hence there should be adequate enabling disclosure in the specification with working example(s).

4. The amount of direction or guidance present:

Examples illustrated in the experimental section or written description offer no guidance or teachings as to how perform the process of making compound of formula Ia when reactive substituents or chemically incompatible substituents are present in the starting material or how transform compound with said R' choices to compound with said R_3 choices.

5. The presence or absence of working examples:

Although examples in specification are limited to R_1 =H and R_3= H groups with no reactive functionality. There are no representative examples showing the viability of the process for plurality of reactive substituents embraced for R_3.

6. The breadth of the claims:

Specification has no support, as noted above, for all compounds generically embraced in the claim language would lead to desired compound of formula Ia with said reactive carbonyl groups and there is also no valid chemical reasoning for one trained in the art to expect that all the reactive carbonyl functional groups would be inert toward the condensation reaction and or the reduction reaction embraced in the process claim 8 and claim 9..

7. The quantity of experimentation needed:

The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired structure, namely compound of formula Ia embraced in the instant claims in view of the prior art teachings of reactivity of these functional groups,.

Thus, factors such as "sufficient working examples", the "level of skill in the art and predictability, etc. have been demonstrated to be sufficiently lacking in the case for the instant claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir.1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claims 10-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating bacterial infection due to , does not reasonably provide enablement for treating any or all bacterial infection on any or all surfaces and preventing adhesion and formation of biofilms by any or all bacteria generically embraced in claim 10 and 19 respectively. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Following reasons apply.

The instant claim 10 and its dependent claim 11-18 are drawn to "antibacterial treatment of surfaces and claim 19 is drawn to "preventing adhesion and formation of biofilms". The scope of the claims includes not only treating or preventing any or all bacterial infections for which there is no enabling disclosure. In addition, the scope of claims include prevention of various bacterial infections such as caused by *Staphylococcus aureus, Cornyebactrium xerosis, Cornyebactrium minuitissimum, Propionibactrium acnes, Proteus vulgaris, Escherichia coli, Klebsiella pneumoniae,*

Salmonella choleraesuls, Pseudomonas aeruginosa, Candida albicans, Aspergillus niger. However, specification provides no enabling disclosure showing that all these genus of bacteria can be prevented with the use of the instant compounds. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Webster's II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the bacterial infection in general claimed herein. Moreover many if not most of bacterial infections such as meningitis, anthrax etc. are very difficult to treat and at present there is no known drug, which can successfully reverse the course of these infectious diseases, despite the fact that there are many antibacterial drugs, which can be used for "treating bacterial infections". Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1094-1099, 2001, wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method of preventing solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the

requirement for undue experimentation. See Snyder et al., J. Med. Liban 48(4): 208-214, 2000 (PubMed Abstract provided), wherein with regards to antibacterial therapies, it is stated that " common bacteria whose susceptibility to antimicrobials is no longer predictable".

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Antibacterial treatment of surfaces and preventing adhesion and formation of biofilms that require inhibiting activity of instant compound.

2) The state of the prior art: Although there are large number antibacterial agents, none of them are claimed or shown to be useful in treating and or preventing any or all bacterial infections. Recent publication expressed that treating disease by the inhibition of is still exploratory. See Snyder et al. cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds for treating and or preventing any or all bacterial infections on any or all surfaces. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of

unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples for treating and or preventing any or all bacterial infections on any or all surfaces and the state of the art is that the effects of bacterial agents based on the disclosed inhibitory activity are unpredictable and at best limited to treating some specific bacterial infection.

6) The breadth of the claims: The instant claims embrace any or all bacterial infections including those yet to be related to like activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards preventing variety of bacterial infections of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 11-19 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 9 and 20-21 are rejected 35 U.S.C 102(b) as being anticipated by Kuefner-Muehl et al., DE 19735800

Kuefner-Muehl et al., teaches several trisubstituted triazines including the pyridyltriazine compounds useful as adenosine antagonist, which include compounds claimed in the instant claims. See entire document especially page 3, formula I and note the definition of R^1, R^2, R^3 and R^4. Note when R^1 is C_1-C_4 alkyl and C_3-C_7 cycloalkyl, R^2 and R^3 is hydrogen or C_1-C_5 alkyl, R^3 is pyridyl and R^4 is C_1-C_4 alkyl and C_3-C_7 cycloalkyl, compounds taught by Kuefner-Muehl et al., include instant compounds when instant R^2 is hydrogen, R^3 is hydrogen or C_1-C_5 alkyl and R^1 is C_1-C_4 alkyl or C_3-C_7 cycloalkyl. See pages 13 and 14 for process of making which include the process

claimed in claim 9. See pages 19 to 45 for various compounds made. Especially see Table 5, examples 104-108 which include instant compound. See also example 3, 4 and 5 for R^2 as alkyl is taught.

Claim 1 is rejected 35 U.S.C 102(b) as being anticipated by Kelarev et al., Khimiya Geterotsiklicheskikh Soedinenii 5, 674-680, 1988, CA 110: 114800, 1989 (CAPLUS Abstract provided)..

Kelarev et al., teaches several substituted pyridyltriazine compounds which include compounds claimed in the instant claims. See the methyl substituted compound in CAPLUS Abstract.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 9 and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuefner-Muehl. DE 19735800

Teachings of Kuefner-Muehl et al., et al., as discussed in the above 102 rejection is incorporated herein. As noted above, Kuefner-Muehl et al., teaches several trisubstituted triazines including the pyridyltriazine compounds useful as adenosine antagonist, which include compounds claimed in the instant claims.

Kuefner-Muehl et al., teaches few examples, compounds 3-5 and 104-108 of the genus embraced in formula I, wherein R^3 is pyridyl.

However, Kuefner-Muehl et al. teaches equivalency of exemplified compounds with those generically claimed. See formula I and note the definition of R_1, R_2, R_3 and R_4.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted in pyridyltriazine as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Allowable Subject Matter

Claims 4-7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Acting Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson whose telephone number is (571) 272-0661.

The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

9/26/2005